Drug Interactions with Weekly Isoniazid/Rifapentine

HP for TB

UNIVERSITY OF LIVERPOOL

Interactions shown are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

Please check www.hiv-druginteractions.org/prescribing_resources for updates to this document.

Comedication	Interaction
A	
Abacavir	↔
Acetazolamide	↔
Aciclovir	↔
Adrenaline (Epinephrine)	↔
Albendazole	↓ⓘ
Amikacin	↔
Aminophylline	↓↑ⓘ
Amitriptyline	↓↑ⓘ
Amlodipine	↓ⓘ
Amodiaquine	↓ⓘ
Amoxicillin	↔
Amphotericin B	↔
Ampicillin	↔
Artemisinin	↓ⓘ
Aspirin (Analgesic)	↔
Aspirin (Anti-platelet)	↔
Atazanavir + ritonavir	↓ⓘ
Atenolol	↔
Atropine	↔
Azathioprine	↔
Azithromycin	↔
B	
Beclometasone	↔
Bedaquiline	↓ⓘ
Bisacodyl	↔
Bleomycin	↔
Bupivacaine	↓ⓘ
C	
Capreomycin	↔
Captopril	↔
Carbamazepine	↑ⓘ
Carbimazole	↔
Cefalexin	↔
Cefotaxime	↔
Ceftazidime	↔
Ceftriaxone	↔
Chloramphenicol	↔
Chlordiazepoxide	↓ⓘ
Chloroquine	↓ⓘ
Chlorpromazine	↔
Cimetidine	↔
Ciprofloxacin	↔
Cisplatin	↔
Clarithromycin	↓ⓘ
Clindamycin	↓ⓘ
Clobetasol	↔
Clofazimine	↔
Cloxacillin	↔
Codeine	↔
Colchicine	↓ⓘ
Cyclophosphamide	↓ⓘ
Cycloserine	↔
Cytarabine	↔
D	
Dacarbazine	↔
Dactinomycin	↔
Dapsone	↓ⓘ
Darunavir + ritonavir	↓ⓘ
Daunorubicin	↔
Dexamethasone	↓ⓘ
Diazepam	↑↓ⓘ
Diclofenac	↓ⓘ
Didanosine	↔
Digoxin	↓ⓘ
Dolutegravir	↓ⓘ
Dopamine	↔
Doxorubicin	↔
Doxycycline	↓ⓘ
E	
Efavirenz	↔
Enalapril	↔
Enoxaparin	↔
Entecavir	↔
Ephedrine	↔
Ergometrine (Ergonovine)	↓ⓘ
Erythromycin	↓ⓘ
Ethambutol	↔
Ethinylestradiol	↓ⓘ
Ethionamide	↔
Etonogestrel (implant)	↓ⓘ
Etonogestrel (vaginal ring)	↓ⓘ
Etoposide	↓ⓘ
Etravirine	↓ⓘ
F	
Fentanyl	↓ⓘ
Filgrastim	↔
Flucloxacillin	↔
Fluconazole	↔
Fludrocortisone	↓ⓘ
Fluocinolone	↔
Fluorouracil	↔
Fluoxetine	↓ⓘ
Fluphenazine	↔
Folic acid	↔
Furosemide	↔
G	
Gabapentin	↔
Gemcitabine	↔
Gentamicin	↔
Glibenclamide (Glyburide)	↓ⓘ
Glipizide	↔
H	
Haloperidol	↓ⓘ
Halothane	↓ⓘ
Heparin	↔
Hydralazine	↔
Hydrochlorothiazide	↔
Hydrocortisone (oral)	↓ⓘ‡
Hydrocortisone (topical)	↔
Hydroxyurea (Hydroxycarbamide)	↔
I	
Ibuprofen	↓ⓘ
Imipenem/Cilastatin	↔
Insulin	↔
Ipratropium bromide	↔
Isoflurane	↔
Isosorbide dinitrate	↑ⓘ
Ivermectin	↓ⓘ

Colour Legend

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- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Text Legend

- ↔ No significant effect
- ↑ Potential increased exposure of the comedication
- ↓ Potential decreased exposure of the comedication
- ⓘ Further information is available in the Notes Section

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Comedication	Interaction
K	
Kanamycin	↔
Ketamine	↓ⓘ
Ketoconazole	↓ⓘ
L	
Labetalol	↔
Lactulose	↔
Lamivudine	↔
Levofloxacin	↔
Levonorgestrel (COC)	↓ⓘ
Levonorgestrel (Emergency Contraception)	↓ⓘ
Levonorgestrel (HRT)	↓ⓘ
Levonorgestrel (implant)	↓ⓘ
Levonorgestrel (IUD)	↔
Levonorgestrel (POP)	↓ⓘ
Levothyroxine	↔
Lidocaine (Lignocaine)	↔
Loperamide	↓ⓘ
Lopinavir/ritonavir	↓ⓘ
Lumefantrine	↓ⓘ
M	
Magnesium supplements	↔
Medroxyprogesterone (depot injection)	↓ⓘ
Medroxyprogesterone (oral)	↓ⓘ
Mefenamic acid	↓ⓘ
Melarsoprol	↔
Meropenem	↔
Metformin	↔
Methotrexate	↔
Methyldopa	↔
Metoclopramide	↔
Metronidazole	↔
Midazolam (oral)	↓ⓘ
Midazolam (parenteral)	↓ⓘ
Misoprostol	↔
Morphine	↔
Moxifloxacin	↔
Multivitamins	↔

Comedication	Interaction
N	
Naloxone	↔
Naproxen	↓ⓘ
Neostigmine	↔
Nevirapine	↓ⓘ
Nicotinamide	↔
Nifedipine	↓ⓘ
Nitrofurantoin	↔
Norethisterone (COC)	↓ⓘ
Norethisterone (HRT)	↓ⓘ
Norethisterone (IM depot)	↓ⓘ
Norethisterone (POP)	↓ⓘ
Norgestimate (COC)	↓ⓘ
Norgestrel (COC)	↓ⓘ
Norgestrel (HRT)	↓ⓘ
Nystatin	↔
O	
Omeprazole	↔
Oxytocin	↔
P	
Paclitaxel	↓ⓘ
Para-aminosalicylic acid	↔
Paracetamol	↑ⓘ
Penicillins	↔
Pethidine (Meperidine)	↑ⓘ
Phenobarbital	↓ⓘ
Phenytoin	↓↑ⓘ
Phytomenadione (Vitamin K)	↔
Piperacillin	↔
Piperaquine	↓ⓘ
Potassium	↔
Praziquantel	↓ⓘ
Prednisolone	↓ⓘ
Prednisone	↓ⓘ
Primaquine	↑ⓘ
Proguanil	↓ⓘ
Promethazine	↔
Propofol	↔ⓘ
Propranolol	↔
Protamine sulphate	↔

Comedication	Interaction
Pyrazinamide	↔
Pyridoxine (Vitamin B6)	↔
Pyrimethamine	↔
Q	
Quinine	↓ⓘ
R	
Raltegravir	↑ⓘ
Ranitidine	↔
Retinol (Vitamin A)	↔
Ritonavir	↓ⓘ
S	
Salbutamol	↔
Sevoflurane	↔
Simvastatin	↓ⓘ
Spironolactone	↔
Stavudine	↔
Streptokinase	↔
Streptomycin	↔
Sulfadoxine	↔
Suramin sodium	↔
Suxamethonium	↔
T	
Tamoxifen	↓ⓘ
Tenofovir-DF	↔
Tetracyclines	↔
Thiamine (Vitamin B1)	↔
Thiopental	↔
Tramadol	↓ⓘ
Trimethoprim/ Sulfamethoxazole	↔
V	
Valproate	↓ⓘ
Vancomycin	↔
Vecuronium	↔
Verapamil	↓ⓘ
Vincristine	↓ⓘ
W	
Warfarin	↓ⓘ
Z	
Zidovudine	↔

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Notes on Red, Amber and Yellow Interactions

Comedication	Notes on Red, Amber and Yellow Interactions
Albendazole	Coadministration has not been studied. In vitro studies have demonstrated that CYP3A4 is involved in the formation of the active metabolite albendazole sulfoxide. When antiepileptics (phenytoin, carbamazepine and phenobarbital) were coadministered with albendazole, significantly reduced levels of the active metabolite albendazole sulfoxide were observed as a result of CYP3A4 induction. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with strongest induction observed at varying times between 2 and 6 days after administration. However, this interaction is not expected to be clinically relevant as the anthelmintic action is thought to be mainly intra-intestinal.
Aminophylline	Coadministration has not been studied. Aminophylline is a complex of theophylline and ethylenediamine and is given for its theophylline activity. Theophylline is mainly metabolized by CYP1A2. Coadministration of isoniazid plus rifampicin has been shown to increase theophylline clearance in the initial phase of treatment and to reduce theophylline clearance afterwards (*Ahn HC et al. Int J Tuberc Lung Dis 2003*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Since the therapeutic range of theophylline is narrow, theophylline serum levels should be monitored closely and adjusted accordingly. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Amitriptyline	Coadministration has not been studied. Amitriptyline is metabolized predominantly by CYP2D6 and CYP2C19. In vitro data indicates that rifapentine does not induce CYP2D6 significantly but can induce CYP2C19. On the other hand, isoniazid inhibits CYP2C19. These opposite effects may mitigate the magnitude of the interaction. Given that amitriptyline metabolism can still occur via CYP2D6, no *a priori* dose adjustment of amitriptyline is needed.
Amlodipine	Coadministration has not been studied. Amlodipine is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, blood pressure should be closely monitored and amlodipine dose adjusted accordingly. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Amodiaquine	Coadministration has not been studied. Amodiaquine is metabolized by CYP2C8. Daily rifampicin was shown to decrease amodiaquine exposure by 66% in healthy volunteers (*Ademisoye A et al. J Explor Res Pharmacol 2018*). In vitro data indicate that rifapentine causes less induction on CYP2C8 compared to rifampicin, therefore, weekly administration of rifapentine is expected to reduce amodiaquine exposure by less than 40%. Closely monitor the clinical and parasitological response of the antimalarial treatment. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Artemisinin	Coadministration has not been studied but is not recommended. Artemisinins undergo metabolism via several CYP450 (CYPs 3A4, 2A6, 2B6). Daily rifampicin was shown to decrease artemether and dihydroartemisinin Cmax by 83% and 78%, respectively (*Lamorde M et al. AIDS 2013*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease artemether and dihydroartemisinin substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of malaria treatment failure.
Atazanavir + ritonavir	Coadministration is not recommended. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease atazanavir substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of developing drug resistance.

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Bedaquiline	Coadministration has not been studied but is not recommended. Bedaquiline is metabolised by CYP3A4. Coadministration of bedaquiline and daily rifampicin was shown to reduce bedaquiline exposure by 52%. Furthermore, a modelling study predicted a significant increase in the metabolite M2 which can increase the risk of QT interval prolongation (*Svensson EM et al. J Antimicrob Chemother 2015*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease bedaquiline substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of malaria treatment failure.
Bupivacaine	Coadministration has not been studied. Bupivacaine is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Bupivacaine dosage should be titrated to meet the individual requirements. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Carbamazepine	Coadministration has not been studied. Carbamazepine is mainly metabolized by CYP3A4. Coadministration of carbamazepine and isoniazid plus rifampicin led to increased carbamazepine levels in a patient likely due to inhibition of carbamazepine metabolism by isoniazid (*Fleenor ME. Chest 1991*). A similar effect could occur with weekly administration of isoniazid/rifapentine. Closely monitor for signs of carbamazepine toxicity including ataxia, nystagmus, diplopia, headache, vomiting. If available, perform carbamazepine TDM and adjust dosage accordingly.
Chlordiazepoxide	Coadministration has not been studied. Chlordiazepoxide is extensively metabolized by hepatic microsomal enzymes. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. A dose adjustment of chlordiazepoxide may be considered as clinically needed. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Chloroquine	Coadministration has not been studied. Chloroquine undergoes CYP mediated metabolism by CYPs 2C8, 3A4 and 2D6, and is also eliminated unchanged via the kidney (50%). In vitro data indicate that rifapentine does not induce CYP2D6 significantly but can induce CYP2C8 and CYP3A4. Weekly administration of isoniazid/rifapentine is expected to decrease chloroquine exposure to a moderate extent due to the multiple elimination pathways. Monitor the efficacy of the antimalarial. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Clarithromycin	Coadministration has not been studied. Clarithromycin undergoes extensive hepatic metabolism. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, isoniazid/rifapentine is expected to decrease clarithromycin exposure but to increase the exposure of 14-OH-clarithromycin, a metabolite that is also microbiologically active. The microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria. Thus, the intended therapeutic effect could be impaired during concomitant administration of rifapentine. Alternatives to clarithromycin, such as azithromycin, should be considered as appropriate. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Clindamycin	Coadministration has not been studied. Clindamycin is metabolized by CYP3A4 and some metabolites have antibacterial activity. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine is expected to decrease clindamycin exposure. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.

Colour Legend

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Drug Interaction Notes for Weekly Isoniazid/Rifapentine

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Colchicine	Coadministration has not been studied. Colchicine is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. A dose adjustment of colchicine may be considered as clinically needed and with caution given that colchicine has a narrow therapeutic index. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Cyclophosphamide	Coadministration has not been studied. Cyclophosphamide is activated to 4-hydroxycyclophosphamide by 2B6 (major), 2C9, and 3A4. The inactivation pathway (minor, 10%) to the neurotoxic chloroacetaldehyde metabolite is mainly by CYP3A4. Weekly administration of isoniazid/rifapentine could either potentially increase the conversion to the active metabolite or increase the amount of drug converted to the inactive neurotoxic metabolite. Careful monitoring of cyclophosphamide efficacy and toxicity is recommended. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Dapsone	Coadministration has not been studied. Coadministration of weekly isoniazid/rifapentine may reduce dapsone exposure due to the inducing effect of rifapentine and increase the formation of dapsone hydroxylamine (a metabolite associated with haemolysis). Monitor for a reduction in dapsone efficacy and signs of haemolytic anaemia. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Darunavir + ritonavir	Coadministration is not recommended. A population pharmacokinetic approach indicates that the coadministration of rifampicin (600 mg once daily) decreases darunavir AUC by 57%, 26%, 1% and 16% when administering darunavir/ritonavir at 800/100 mg once daily, 1200/200 mg once daily, 1600/200 mg once daily, and 800/100 mg twice daily. Increase in darunavir/ritonavir dose to overcome the interaction with rifampicin led to unacceptable hepatotoxicity in people living with HIV (*Ebrahim I et al. J Antimicrob Chemother 2020*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease darunavir substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of developing drug resistance.
Dexamethasone	Coadministration has not been studied. Dexamethasone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. A dose adjustment of dexamethasone may be considered as clinically needed. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Diazepam	Coadministration has not been studied. Diazepam is metabolized to nordiazepam by CYP3A4 and 2C19 and additionally to temazepam mainly by CYP3A4. In vitro data indicate that rifapentine induces CYP2C19 and CYP3A4. On the other hand, isoniazid inhibits CYP2C19 and CYP3A4. The direction of the interaction is difficult to predict but the opposite effects on CYPs may mitigate the magnitude of the interaction. Monitor clinical effect and for signs of toxicity. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Diclofenac	Coadministration has not been studied. Diclofenac is hydroxylated to several metabolites with the major metabolite (4-hydroxy diclofenac) being formed by CYP2C9. In addition, some diclofenac is directly glucuronidated by UGT2B7. Daily rifampicin was shown to decrease celecoxib (another CYP2C9 substrate) exposure by 64% in healthy volunteers (*Jayasagar G et al. Drug Metabol Drug Interact 2003*). In vitro data indicate that rifapentine causes less induction on CYP2C9 compared to rifampicin and does not induce significantly UGTs, therefore, weekly administration of rifapentine is expected to reduce diclofenac exposure by less than 40%. No *a priori* dose adjustment of diclofenac is needed.

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Digoxin	Coadministration has not been studied. Coadministration of rifampicin was shown to reduce substantially digoxin exposure due to induction of intestinal P-gp (*Greiner B et al. J Clin Invest 1999*). Weekly administration of isoniazid/rifapentine is also expected to reduce digoxin exposure. Monitor serum digoxin concentrations and adjust dosage accordingly. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Dolutegravir	Coadministration of dolutegravir (50 mg once daily) with once weekly isoniazid/rifapentine (900/900 mg) decreased dolutegravir AUC by 26%. The overall geometric mean ratio for dolutegravir Ctrough with and without once weekly isoniazid/rifapentine was 0.53 (90% CI 0.49-0.56). The geometric mean ratio varied by day with values of 0.77 (0.71-0.84) 1 day after isoniazid/rifapentine dosing, 0.36 (0.32-0.4) 2 days after dosing and 0.44 (0.4-0.48) 5-6 days after dosing. Importantly, geometric mean Ctrough were above 300 ng/mL at all visits over the 12 weeks of co-treatment and HIV viral load remained suppressed in all participants. The treatment was well tolerated. The authors concluded that no dose adjustment of dolutegravir is needed when coadministered with once weekly isoniazid/rifapentine (*Dooley KE et al. Lancet HIV 2020*). However, dolutegravir 50 mg twice daily should be considered in individuals with suspicion of viral failure or blips.
Doxycycline	Coadministration has not been studied. Although doxycycline is not appreciably metabolized by the liver, its clearance has been shown to be substantially increased when administered with inducers such as rifapentine which may result in sub-therapeutic concentrations. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Ergometrine (Ergonovine)	Coadministration has not been studied. Ergometrine is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. A dose adjustment of ergometrine may be considered as clinically needed and with caution given that ergometrine has a narrow therapeutic index. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Erythromycin	Coadministration has not been studied. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Weekly administration of isoniazid/rifapentine may decrease erythromycin concentrations and efficacy. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Ethinylestradiol	Coadministration has not been studied. Ethinylestradiol is mainly metabolized by hydroxylation. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Etonogestrel (implant)	Coadministration has not been studied. Etonogestrel is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Etonogestrel (vaginal ring)	Coadministration has not been studied. Etonogestrel is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.

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Etoposide	Coadministration has not been studied. Etoposide is partly glucuronidated by UGT1A1 and partly metabolized by CYP3A4 to reactive catechol metabolites. Conversion to reactive metabolites can also be mediated by prostaglandin synthase or myeloperoxidase. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine may increase etoposide clearance and reduce efficacy. Monitor clinical effect. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Etravirine	Coadministration is not recommended. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease etravirine substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of developing drug resistance.
Fentanyl	Coadministration has not been studied. Fentanyl undergoes extensive CYP3A4 metabolism. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine could decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using fentanyl with CYP3A4 inducers, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur. Discontinuation of a concomitantly used CYP3A4 inducer may increase in fentanyl concentrations which could result in a fatal overdose of fentanyl. When discontinuing CYP3A4 inducers in fentanyl-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of fentanyl until stable drug effects are achieved.
Fludrocortisone	Coadministration has not been studied. Fludrocortisone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. A dose adjustment of fludrocortisone may be considered as clinically needed. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Fluoxetine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Fluoxetine is metabolized by CYPs 2D6 and 2C9 and to a lesser extent by CYPs 2C19 and 3A4 to form norfluoxetine. In vitro data indicate that isoniazid/rifapentine do not significantly inhibit or induce CYP2D6. In vitro data indicate that rifapentine is a less potent inducer of CYP2C9 compared to rifampicin. Based on these considerations, the magnitude of the interaction is predicted to be limited so that no *a priori* dose adjustment of fluoxetine is needed.
Glibenclamide (Glyburide)	Coadministration has not been studied. Glibenclamide is metabolized by CYP3A4 and to a lesser extent by CYP2C9. Daily rifampicin was shown to decrease glibenclamide exposure by 39% in healthy volunteers. Rifampicin impaired the blood glucose lowering of glibenclamide (*Niemi M et al. Clin Pharmacol Ther 2001*). Rifapentine causes less induction on CYP2C9 compared to rifampicin therefore weekly administration of rifapentine would not be expected to significantly alter the pharmacodynamic effect. Glucose monitoring is still advised.
Haloperidol	Coadministration has not been studied. Haloperidol undergoes glucuronidation (UGT2B7 > 1A4, 1A9), carbonyl reduction and oxidative metabolism (CYP3A4, CYP2D6). Weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Furthermore, in vitro data indicate that isoniazid/rifapentine do not significantly inhibit or induce CYP2D6. Considering the multiple metabolic pathway and considering that some pathways are not affected, the magnitude of the interaction is predicted to be mitigated. No *a priori* dosage adjustment is needed.

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

Please check www.hiv-druginteractions.org/prescribing_resources for updates to this document.

Comedication	Notes on Red, Amber and Yellow Interactions
Halothane	Coadministration has not been studied. Halothane undergoes both oxidative and reductive metabolism by cytochromes. In vitro data have shown that oxidation occurs mainly via CYP2E1 and to a lesser extent CYP2A6 and reduction via CYP2A6 and CYP3A4. Isoniazid induces CYP2E1 and therefore could reduce halothane concentrations. Halothane dosage should be titrated to meet the individual requirements.
Hydrocortisone (oral)	Coadministration has not been studied. Hydrocortisone is metabolized by CYP3A4. Hydrocortisone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. A dose adjustment of hydrocortisone may be considered as clinically needed. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Ibuprofen	Coadministration has not been studied. Ibuprofen is metabolized mainly by CYP2C9. Daily rifampicin was shown to decrease celecoxib (another CYP2C9 substrate) exposure by 64% in healthy volunteers (*Jayasagar G et al. Drug Metabol Drug Interact 2003*). In vitro data indicate that rifapentine causes less induction on CYP2C9 compared to rifampicin therefore weekly administration of rifapentine is expected to reduce ibuprofen exposure by less than 40%. No *a priori* dose adjustment of ibuprofen is needed.
Isosorbide dinitrate	Coadministration has not been studied. In vitro studies suggest that CYP3A4 has a role in nitric oxide formation from isosorbide dinitrate. Inducers of CYP3A4 such as rifapentine may therefore increase production of the active substance nitric oxide. The clinical relevance of this potential interaction is unknown.
Ivermectin	Coadministration has not been studied. Ivermectin is predominantly metabolised by CYP3A4. There is potential for rifapentine to decrease levels of ivermectin via induction of CYP3A4, however the clinical relevance of this hypothetical interaction is low given that ivermectin is administered as a single dose.
Ketamine	Coadministration has not been studied. Ketamine is metabolised mainly by CYP3A4 and to a lesser extent by CYPs 2B6 and 2C9 in the range of concentrations used in anaesthesia. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Ketamine dosage should be titrated to meet the individual requirements. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Ketoconazole	Coadministration has not been studied but is not recommended. Ketoconazole is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can decrease ketoconazole concentrations substantially and in an intermittent manner thereby impairing its efficacy.
Levonorgestrel (COC)	Coadministration has not been studied. Levonorgestrel is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Levonorgestrel (Emergency Contraception)	Coadministration has not been studied. The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers like rifapentine. Concomitant administration of the inducer efavirenz has been found to reduce plasma levels of levonorgestrel exposure by around 50% (*Carten M et al. Infect Dis Obstet Gynecol 2012*). The Faculty of Sexual and Reproductive Healthcare Clinical Guidance states that the use of copper intrauterine device (Cu-IUD) is the most effective method for emergency contraception in women receiving an enzyme-inducing drug and that women who are not eligible for Cu-IUD should be offered a total of 3 mg levonorgestrel as a single dose for emergency contraception. Note: doubling the standard dose is outside the product license and there is limited evidence in relation to the efficacy.

Colour Legend

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- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Red, Amber and Yellow Interactions
Levonorgestrel (HRT)	Coadministration with levonorgestrel as hormone replacement therapy (HRT) has not been studied. Levonorgestrel is metabolized by CYP3A4 and is glucuronidated to a minor extent. Coadministration is predicted to decrease levonorgestrel exposure due to rifapentine inducing effect. Monitor for signs of hormone deficiency.
Levonorgestrel (implant)	Coadministration has not been studied. Levonorgestrel is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Levonorgestrel (POP)	Coadministration has not been studied. Levonorgestrel is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Loperamide	Coadministration has not been studied. Loperamide is mainly metabolized by CYP3A4 and CYP2C8. Weekly administration of isoniazid/rifapentine is expected to decrease loperamide exposure due to CYP3A4 and CYP2C8 induction by rifapentine. If needed, consider increasing loperamide dose. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Lopinavir/ritonavir	Coadministration is not recommended as it may cause significant decreases in lopinavir/ritonavir concentrations leading to loss of therapeutic effect and possible development of resistance. Adequate exposure to lopinavir/ritonavir may be achieved when a higher dose of lopinavir/ritonavir (400/400 mg twice daily) is used but this is associated with a higher risk of liver and gastrointestinal toxicity. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease lopinavir/ritonavir substantially and in an intermittent manner, consider a higher dose of lopinavir/ritonavir (400/400 mg twice daily if coadministration is judged strictly necessary.
Lumefantrine	Coadministration has not been studied but is not recommended. Lumefantrine undergoes CYP3A4 metabolism. A population pharmacokinetic meta-analysis using individual participant data from 10 studies with 6,100 lumefantrine concentrations showed that lumefantrine exposure decreased 59% in the patients with rifampicin-based antituberculosis treatment. Simulations showed that individuals on concomitant rifampicin have 80% probability of day 7 concentrations <200 ng/ml, a threshold associated with an increased risk of treatment failure (*Francis J et al. Antimicrob Agents Chemother 2020*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can decrease lumefantrine concentrations substantially and in an intermittent manner leading to increased risk of malaria treatment failure.
Medroxyprogesterone (depot injection)	Coadministration has not been studied. Medroxyprogesterone is metabolized by CYP3A4. Medroxyprogesterone clearance was shown to be increased in presence of rifampicin plus efavirenz leading to the recommendation to shorten the interval between medroxyprogesterone injections to 8-10 weeks (*Mngqibisa R et al. Clin Infect Dis 2020*). Similarly, weekly administration of isoniazid/rifapentine may increase the elimination of medroxyprogesterone. The interaction may be overcome by shortening the interval between injections. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.

Colour Legend

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- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Red, Amber and Yellow Interactions
Medroxyprogesterone (oral)	Coadministration with medroxyprogesterone as hormone replacement therapy (HRT) has not been studied. Medroxyprogesterone is metabolized by CYP3A4. Coadministration is predicted to decrease medroxyprogesterone exposure due to rifapentine inducing effect. Monitor for signs of hormone deficiency.
Mefenamic acid	Coadministration has not been studied. Mefenamic acid is metabolized by CYP2C9 (and additionally glucuronidated by UGT2B7 and 1A9). Daily rifampicin was shown to decrease celecoxib (another CYP2C9 substrate) exposure by 64% in healthy volunteers (*Jayasagar G et al. Drug Metabol Drug Interact 2003*). In vitro data indicate that rifapentine causes less induction on CYP2C9 compared to rifampicin therefore weekly administration of rifapentine is expected to reduce mefenamic acid exposure less than 40%. No *a priori* dose adjustment of mefenamic acid is needed.
Midazolam (oral)	Coadministration has not been studied. Midazolam is metabolized by CYP3A4. Rifampicin has been shown to reduce the plasma concentrations of oral midazolam by 96% (*Backman JT et al. Clin Pharmacol Ther 1996*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Midazolam dosage should be adjusted to meet the individual requirements. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Midazolam (parenteral)	Coadministration has not been studied. Midazolam is metabolized by CYP3A4. Rifampicin has been shown to reduce the plasma concentrations of intravenous midazolam by 60% (*Midazolam SmPC, Advanz Pharma, 2018*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Midazolam dosage should be adjusted to meet the individual requirements. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Naproxen	Coadministration has not been studied. Naproxen is mainly metabolized by O-dealkylation via CYP2C9 and by direct glucuronidation. Daily rifampicin was shown to decrease celecoxib (another CYP2C9 substrate) exposure by 64% in healthy volunteers (*Jayasagar G et al. Drug Metabol Drug Interact 2003*). In vitro data indicate that rifapentine causes less induction on CYP2C9 compared to rifampicin. Furthermore, weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Thus, weekly administration of rifapentine is expected to reduce naproxen exposure by less than 40%. No *a priori* dose adjustment of naproxen is needed. Isoniazid does not inhibit or induce UGTs or CYP2C9.
Nevirapine	Coadministration is not recommended as it may cause significant decreases in nevirapine concentrations leading to loss of therapeutic effect and possible development of resistance. Coadministration of nevirapine and rifampicin significantly decreased nevirapine AUC (58%), Cmax (50%) and Cmin (68%) (*Viramune SmPC, Boehringer Ingelheim, 2019*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease nevirapine substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of developing drug resistance.
Nifedipine	Coadministration has not been studied. Nifedipine is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Blood pressure should be closely monitored and nifedipine dose adjusted accordingly. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Norethisterone (COC)	Coadministration has not been studied. Norethisterone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.

Colour Legend

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- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Red, Amber and Yellow Interactions
Norethisterone (HRT)	Coadministration with norethisterone as hormone replacement therapy (HRT) has not been studied. Norethisterone is metabolized by CYP3A4. Coadministration is predicted to decrease norethisterone exposure due to rifapentine inducing effect. Monitor for signs of hormone deficiency.
Norethisterone (IM depot)	Coadministration with a norethisterone IM depot injection has not been studied. Norethisterone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Norethisterone (POP)	Coadministration has not been studied. Norethisterone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Norgestimate (COC)	Coadministration has not been studied. Norgestimate is deacetylated to the active metabolite norelgestromin which is then metabolised to norgestrel, possibly by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Norgestrel (COC)	Coadministration has not been studied. Norgestrel is a racemic mixture with levonorgestrel being biologically active. Levonorgestrel is metabolized by CYP3A4 and is glucuronidated to a minor extent. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can potentially reduce contraceptive efficacy. Barrier contraception must be used during and up to 2 weeks after isoniazid/rifapentine treatment cessation due to the persisting inducing effect upon discontinuation of an inducer.
Norgestrel (HRT)	Coadministration with norgestrel as hormone replacement therapy (HRT) has not been studied. Norgestrel is a racemic mixture with levonorgestrel being biologically active. Levonorgestrel is metabolized by CYP3A4 and is glucuronidated to a minor extent. Coadministration is predicted to decrease norgestrel exposure. Monitor for signs of hormone deficiency.
Paclitaxel	Coadministration has not been studied. Paclitaxel is primarily metabolized by CYP2C8 and to a lesser extent by CYP3A4. In vitro data indicate that rifapentine induces CYP2C8 and CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. The label does not recommend to administer paclitaxel with medicines known to inducer either CYP2C8 or CYP3A4 because the efficacy may be compromised due to lower paclitaxel exposure.
Paracetamol	Several cases of hepatotoxicity have been reported in patients receiving TB drugs. This interaction could relate to the inducing effect of isoniazid on CYP2E1 leading to a higher proportion of paracetamol being converted to toxic metabolites (*Nolan CM et al. Chest 1994*). Thus, the normal daily analgesic dosage of 4 g may not be safe. The dose of paracetamol should be limited because some people risk possible paracetamol induced liver toxicity. Furthermore, paracetamol may increase isoniazid exposure as it inhibits N-acetyltransferase (*Rothen JP et al. Pharmacogenetics 1998*).

Colour Legend

No clinically significant interaction expected.

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Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Red, Amber and Yellow Interactions
Pethidine	Coadministration has not been studied. Meperidine is hydrolyzed to meperidinic acid by liver carboxylesterases and demethylated by CYP (unknown isoenzyme) to normeperidine which may be further hydrolyzed to normeperidinic acid and subsequently conjugated. The metabolite normeperidine is neurotoxic. Coadministration of meperidine and rifapentine can potentially increase the amount of the neurotoxic metabolite and thereby increase the risk of seizures.
Phenobarbital	Coadministration has not been studied. Phenobarbital is partly metabolized in the liver. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine may reduce phenobarbital concentrations. Monitor the therapeutic response and adjust phenobarbital dosage if needed. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Phenytoin	Coadministration has not been studied. Phenytoin is metabolized by CYP2C9 and CYP2C19. Rifapentine is an inducer of CYP2C9 and CYP2C19 whereas isoniazid inhibits CYP2C19. If rifapentine and isoniazid are given concomitantly, the direction of the interaction will depend on the isoniazid acetylator status of the patient. Fast acetylators may need an increased phenytoin dosage whereas slow acetylators may need a dose reduction. Patients should be monitored closely as the direction of the interaction is unpredictable. If available, perform phenytoin TDM and adjust dosage accordingly.
Piperaquine	Coadministration has not been studied but is not recommended. Piperaquine is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can decrease piperaquine concentrations substantially and in an intermittent manner thereby impacting its efficacy.
Praziquantel	Coadministration has not been studied. In vitro, praziquantel is metabolised predominantly by CYP3A4. Data with liver enzyme inducers phenytoin, carbamazepine and rifampicin showed a significant decrease in exposure to praziquantel when co-administered. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine may reduce praziquantel concentrations and its efficacy. Monitor the therapeutic response and adjust praziquantel dosage if needed. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Prednisolone	Coadministration has not been studied. Prednisolone is metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine may reduce prednisolone concentrations and its therapeutic efficacy. Increase prednisolone dosage if needed. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Prednisone	Coadministration has not been studied. Prednisone is converted to the active metabolite prednisolone by 11-B-hydroxydehydrogenase. Prednisolone is then metabolized by CYP3A4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine may reduce prednisone concentrations and its therapeutic efficacy. Increase prednisone dosage if needed. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Primaquine	Coadministration has not been studied. Primaquine is metabolised mainly through a non-CYP mediated mechanism and only a small fraction of the drug is believed to be metabolised through CYP450. The oxidative metabolites (formed through metabolism by CYPs 2E1, 2B6, 2D6, 3A4 and 1A2) rather than the parent drug are primarily responsible for the haemolytic effects of primaquine. Isoniazid/rifapentine could potentially increase the amount of haemotoxic metabolites. Caution should be used when combining these drugs

Colour Legend

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- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Red, Amber and Yellow Interactions
Proguanil	Coadministration has not been studied. Proguanil is partly excreted unchanged and partly metabolized to its more active metabolite cycloguanil by CYP2C19 and to a lesser extent by CYP3A4. Isoniazid inhibits CYP2C19 whereas rifapentine induces this enzyme. These opposite effects may mitigate the magnitude of the interaction. Closely monitor the clinical and parasitological response of the antimalarial treatment. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Propofol	Coadministration has not been studied. Propofol is glucuronidated via UGT1A9, UGT1A8 and is oxidized mainly via CYP2B6. The literature reports cases of profound hypotension after anaesthesia induction with propofol in patients treated with rifampicin (*Mirzakhani H et al. Anesth Analg. 2013*). The mechanism of this interaction is unknown and therefore a similar effect cannot be excluded with rifapentine. Use with caution and close monitoring.
Quinine	Coadministration has not been studied but is not recommended. Quinine is extensively metabolized by CYP3A4. The relationships between the pharmacokinetic properties of quinine during a 7-day treatment course and the therapeutic response were studied in 30 adult patients with uncomplicated falciparum malaria with and without co-treatment with rifampicin. During the 28-day monitoring period, six patients had recrudescent infections (two were treated with quinine alone and four were treated with quinine plus rifampicin). Rifampicin led to a reduction in quinine concentrations in blood and a high treatment failure rate (*Pukrittayakamee S et al. Antimicrob Agents Chemother 2003*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can decrease quinine concentrations substantially and in an intermittent manner leading to increased risk of malaria treatment failure.
Raltegravir	Coadministration of raltegravir (400 mg twice daily) and the weekly administration of rifapentine (900 mg) was evaluated in healthy volunteers. The geometric mean ratios for raltegravir AUC and Ctrough were increased by 71% and decreased by 12%, respectively, in presence of rifapentine. The authors of the study conclude that the increase in raltegravir exposure was safe and tolerable. Raltegravir can be coadministered with once weekly isoniazid/rifapentine without any dose adjustment (*Weiner M et al. J Antimicrob Chemother 2014*).
Ritonavir	Coadministration is not recommended. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Given that weekly isoniazid/rifapentine could decrease ritonavir substantially and in an intermittent manner, concurrent administration should be avoided due to the risk of developing drug resistance.
Simvastatin	Coadministration has not been studied. Simvastatin is a sensitive CYP3A4 substrate. Coadministration with rifampicin reduced simvastatin AUC by 87% (*Kyrklund C, et al. Clin Pharmacol Ther. 2000*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, weekly administration of isoniazid/rifapentine can reduce simvastatin exposure. Cholesterol levels should be periodically monitored and dosage of simvastatin increases if needed.
Tamoxifen	Coadministration has not been studied but could potentially decrease the levels of tamoxifen and metabolites via induction of CYP3A4 and thereby reduce the efficacy of tamoxifen. Tamoxifen metabolism occurs mostly via two pathways: the formation of N-desmethyltamoxifen (via mainly CYP3A4 and CYP3A5) is the main route (92%) and the formation of 4-hydroxytamoxifen (via CYP2D6 > 2C9/19, CYP3A4 and CYP2B6) is a minor route (7%). Coadministration of rifampicin, an inducer of cytochromes, markedly reduced tamoxifen and its metabolites concentrations (*Binkhorst L, et al. Clin Pharmacol Ther. 2012*). Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Monitor response to chemotherapy. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.

Colour Legend

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- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

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Comedication	Notes on Red, Amber and Yellow Interactions
Tramadol	Coadministration has not been studied. Tramadol is metabolized by N-demethylation (CYP3A4 and CYP2B6) and to an active metabolite which is more potent than the parent compound by O-demethylation (CYP2D6). Daily rifampicin has been shown to reduce tramadol exposure (*Saarikoski T et al. Eur J Clin Pharmacol 2013*). Weekly isoniazid/rifapentine may reduce tramadol exposure but may not affect the metabolic pathway leading to the more potent active metabolite as isoniazid/rifapentine do not inhibit or induce CYP2D6. No *a priori* dosage adjustment is recommended. Monitor the analgesic effect and adjust tramadol dose if needed.
Valproate	Coadministration has not been studied. Valproate is mainly glucuronidated by UGTs 1A6, 1A9 and 2B7 and metabolized by CYP2C9 and CYP2C19. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, isoniazid/rifapentine may reduce valproate exposure. Valproate dosage adjustment may be necessary. Monitor valproate levels where possible.
Verapamil	Coadministration has not been studied. Verapamil is metabolized by CYP3A4 and is an inhibitor of this same enzyme. Verapamil is unlikely to alter isoniazid/rifapentine concentrations as these agents do not undergo CYP3A4 mediated metabolism. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, isoniazid/rifapentine may reduce verapamil exposure. Blood pressure should be closely monitored and verapamil dose adjusted accordingly. Note: the inducing effect is expected to last up to 2 weeks following cessation of rifapentine.
Vincristine	Coadministration has not been studied. Vincristine is metabolized by CYP3A5/4. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration. Thus, isoniazid/rifapentine may reduce vincristine concentrations. Monitor response to chemotherapy. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.
Warfarin	Coadministration has not been studied. Warfarin is a mixture of enantiomers which are metabolized by different cytochromes. R-warfarin is primarily metabolized by CYP1A2 and 3A4. S-warfarin (more potent) is metabolized by CYP2C9. Weekly administration of isoniazid/rifapentine was shown to cause a time dependent induction with the strongest induction observed at varying times between 2 and 6 days after administration Thus, weekly administration of isoniazid/rifapentine may induce the hepatic metabolism of warfarin through induction of CYP3A4 and CYP2C9. Closely monitor INR and adjust warfarin dose as needed. Note: the inducing effect is expected to last up to 2 weeks after cessation of rifapentine.

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

Please check www.hiv-druginteractions.org/prescribing_resources for updates to this document.

Notes on Green Interactions

Comedication	Notes on Green Interactions
Abacavir	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Abacavir is eliminated by alcohol dehydrogenase and by glucuronidation. Weekly administration of rifapentine did not reduce the exposure of the substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Acetazolamide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Acetazolamide is primarily excreted unchanged via the kidneys.
Aciclovir	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as aciclovir is eliminated renally via glomerular filtration and active renal secretion by OAT1. Isoniazid/rifapentine do not interfere with this elimination pathway.
Adrenaline (Epinephrine)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as adrenaline is rapidly inactivated, mostly in the liver by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Isoniazid/rifapentine do not interfere with this elimination pathway.
Amikacin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as amikacin is eliminated renally by glomerular filtration.
Amoxicillin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Amoxicillin is mainly eliminated unchanged in the kidney.
Amphotericin B	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as amphotericin is not appreciably metabolized and is eliminated to a large extent in the bile.
Ampicillin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ampicillin is predominantly eliminated unchanged via renal pathways.
Aspirin (Analgesic)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Aspirin is rapidly deacetylated to salicylic acid and then further metabolized mainly by glucuronidation. Once weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Aspirin (Anti-platelet)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Aspirin is rapidly deacetylated to salicylic acid and then further metabolized mainly by glucuronidation. Once weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Atenolol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as atenolol is mainly eliminated unchanged by the kidney, both by glomerular filtration and active secretion via the renal transporters OCT2 and MATE1.
Atropine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as atropine is excreted unchanged via the kidneys up to 50%.
Azathioprine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Azathioprine is metabolized to 6-mercaptopurine which is further inactivated by xanthine oxidase and thiopurine methyltransferase. Isoniazid/rifapentine do not interfere with this elimination pathway.
Azithromycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Azithromycin is mainly eliminated via biliary excretion.

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

Please check www.hiv-druginteractions.org/prescribing_resources for updates to this document.

Comedication	Notes on Green Interactions
Beclometasone	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Beclometasone is a pro-drug which is not metabolised by CYP450 but is hydrolysed via esterase enzymes to the highly active metabolite beclometasone-17-monopropionate.
Bisacodyl	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Bisacodyl is converted to an active metabolite by intestinal and bacterial enzymes. Absorption from the gastrointestinal tract is minimal and the small amount absorbed is excreted in the urine as the glucuronide.
Bleomycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Bleomycin is inactivated by a cytosolic enzyme, bleomycin hydrolase, and two thirds of the administered drug is excreted unchanged in urine, probably by glomerular filtration.
Capreomycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Capreomycin is predominantly excreted via the kidneys as unchanged drug.
Captopril	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Captopril is largely excreted in the urine (40-50% as unchanged drug, the rest as disulfide and other metabolites).
Carbimazole	Coadministration has not been studied, but based on metabolism and clearance a clinically significant interaction is unlikely. Carbimazole is a pro-drug which undergoes rapid and virtually complete metabolism to the active metabolite, thiamazole (also known as methimazole). Despite this potential hepatic metabolism very few data exist on carbimazole drug interactions and a marked interaction is not expected.
Cefalexin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Cefalexin is predominantly eliminated unchanged via the kidneys
Cefotaxime	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Cefotaxime is predominantly eliminated unchanged via the kidneys.
Ceftazidime	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ceftazidime is predominantly eliminated unchanged via renal glomerular filtration.
Ceftriaxone	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ceftriaxone is eliminated mainly as unchanged drug; approximately 60% of the dose being excreted in the urine, almost exclusively by glomerular filtration, and the remainder via the biliary and intestinal tracts.
Chloramphenicol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Chloramphenicol is mostly glucuronidated. Once weekly administration of rifapentine did not reduce the exposure of the pure UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Chloramphenicol inhibits CYPs but this is unlikely to impact isoniazid/rifapentine as these agents do not undergo CYP-mediated metabolism.
Chlorpromazine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Chlorpromazine is metabolized mainly by CYP2D6, but also CYP1A2. In vitro data indicated that isoniazid/rifapentine do not significantly inhibit or induce CYP2D6 or CYP1A2.
Cimetidine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Coadministration of isoniazid/rifapentine with medicinal products that alter gastric pH are not expected to affect isoniazid/rifapentine absorption (*Lin MY et al. Int J Tuberc Lung Dis 2010*).
Ciprofloxacin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ciprofloxacin is primarily eliminated unchanged by the kidneys by glomerular filtration and tubular secretion via OAT3. It is also metabolized and partially cleared through the bile and intestine.

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

Please check www.hiv-druginteractions.org/prescribing_resources for updates to this document.

Comedication	Notes on Green Interactions
Cisplatin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as cisplatin is eliminated renally.
Clobetasol	Coadministration has not been studied but based on metabolism and clearance a clinically relevant drug interaction is unlikely with the topical use of clobetasol.
Clofazimine	Coadministration has not been studied but based on metabolism and clearance a clinically relevant drug interaction is unlikely. Clofazimine is largely excreted unchanged in the faeces, both as unabsorbed drug and via biliary excretion.
Cloxacillin	Coadministration has not been studied but based on metabolism and clearance a clinically relevant drug interaction is unlikely. Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion.
Codeine	Coadministration has not been studied but based on metabolism and clearance a clinically relevant drug interaction is unlikely. Codeine is converted to morphine (active metabolite) via CYP2D6 and inactivated to codeine-6-glucuronide via glucuronidation (major pathway) as well as to norcodeine via CYP3A4. In vitro data indicate that isoniazid/rifapentine do not significantly inhibit or induce CYP2D6. Furthermore, the weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Cycloserine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Cycloserine is predominantly excreted renally via glomerular filtration.
Cytarabine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as cytarabine is metabolized by cytidine deaminase. Isoniazid/rifapentine do not interfere with this elimination pathway.
Dacarbazine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Dacarbazine undergoes activation to MTIC primarily via CYP1A2 and to a lesser extent by CYP2E1, with CYP1A1 having a role in extrahepatic metabolism. Isoniazid/rifapentine do not significantly inhibit or induce CYP1A2. Isoniazid induces CYP2E1 but the clinical relevance of this effect is unclear since CYP2E1 plays a minor role in dacarbazine elimination.
Dactinomycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Dactinomycin is minimally metabolized.
Daunorubicin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Daunorubicin undergoes metabolism in the liver and other tissues mainly by cytoplasmic aldo-keto reductases. Isoniazid/rifapentine does not interfere with this elimination pathway.
Didanosine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as didanosine is mainly excreted in urine.
Dopamine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction unlikely. Dopamine is metabolised in the liver, kidneys, and plasma by monoamine oxidase (MAO is) and catechol-O-methyltransferase to inactive compounds. Isoniazid/rifapentine do not interfere with this elimination pathway.
Doxorubicin	Coadministration has not been studied, but based on metabolism and clearance a clinically significant interaction is unlikely. Doxorubicin is mainly eliminated in the bile.
Efavirenz	Coadministration of efavirenz and a weekly dose of isoniazid/rifapentine did not significantly alter efavirenz exposure. Efavirenz AUC ratio after 3 weekly doses of isoniazid/rifapentine versus efavirenz administered alone was 0.86 (95% CI 0.79-0.93). Coadministration is possible with no dose adjustment (*Farenc C et al. CROI 2014*).

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Green Interactions
Enalapril	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Enalapril is hydrolysed to enalaprilat which is eliminated renally, possibly via OATs.
Enoxaparin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Enoxaparin does not undergo cytochrome metabolism but is desulphated and depolymerised in the liver, and is excreted predominantly renally. Isoniazid/rifapentine do not interfere with this elimination pathway.
Entecavir	Coadministration has not been studied but based on the metabolism and clearance a clinically significant interaction is unlikely. Entecavir is eliminated renally via glomerular filtration and active renal secretion by both organic anion and cation transporters.
Ephedrine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ephedrine is predominantly eliminated unchanged via the kidneys.
Ethambutol	Coadministration of efavirenz and ethambutol alone has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ethambutol is partly metabolized by alcohol dehydrogenase (20%) and partly eliminated unchanged in the faeces (20%) and in the urine (50%). Isoniazid/rifapentine do not interfere with this elimination pathway.
Ethionamide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Ethionamide is extensively metabolized in the liver; animal studies suggest involvement of flavin-containing monooxygenases. Isoniazid/rifapentine do not interfere with this pathway.
Filgrastim	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Filgrastim is eliminated mainly by neutrophil-mediated clearance and renal excretion.
Flucloxacillin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Flucloxacillin is mainly eliminated renally partly by glomerular filtration and partly by active secretion via OAT1.
Fluconazole	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Fluconazole is mainly eliminated renally by glomerular filtration. Fluconazole does inhibit CYPs 2C9 and 3A4 but no effect is expected on isoniazid or rifapentine as these agents do not undergo CYP mediated metabolism.
Fluocinolone	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely with the topical use of fluocinolone.
Fluorouracil	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Fluorouracil is metabolised via the same mechanisms as endogenous uracil, including via dihydropyrimidine dehydrogenase. There is therefore little potential for an interaction with isoniazid/rifapentine via modulation of, or competition for metabolic pathways.
Fluphenazine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Fluphenazine is metabolised by CYP2D6. In vitro data indicate that isoniazid/rifapentine do not significantly inhibit or induce CYP2D6.
Folic acid	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Folic acid is metabolized to dihydrofolic acid and tetrahydrofolic acid with the aid of reduced diphosphopyridine nucleotide and folate reductases. Isoniazid/rifapentine do not interfere with this pathway.

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Green Interactions
Furosemide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Furosemide is glucuronidated mainly in the kidney (UGT1A9) and to a lesser extent in the liver (UGT1A1). A large proportion of furosemide is also eliminated unchanged renally. Weekly administration of rifapentine did not reduce the exposure of the UGT1A1 substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Gabapentin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as gabapentin is exclusively eliminated unchanged in the urine.
Gemcitabine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Gemcitabine is metabolized in the liver by cytidine deaminase to an inactive metabolite.
Gentamicin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Gentamicin is predominantly eliminated unchanged via the kidneys.
Glipizide	Coadministration has not been studied. Glipizide is metabolized by CYP2C9. Daily rifampicin was shown to decrease glipizide exposure by 22% in healthy volunteers, this decrease had no effect on blood glucose (*Niemi M et al. Clin Pharmacol Ther 2001*). In vitro data indicate that rifapentine causes less induction on CYP2C9 compared to rifampicin therefore weekly administration of rifapentine is unlikely to alter glipizide effect.
Heparin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Heparin is thought to be eliminated via the reticuloendothelial system.
Hydralazine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Hydralazine undergoes acetylation. Hydralazine was shown to inhibit CYPs but no effect is expected on isoniazid/rifapentine as these drugs do not undergo CYP mediated metabolism.
Hydrochlorothiazide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Hydrochlorothiazide is not metabolised and is cleared by the kidneys via OAT1.
Hydrocortisone (topical)	Coadministration has not been studied but no clinically relevant drug interactions are expected with the topical use of hydrocortisone.
Hydroxyurea (Hydroxycarbamide)	Coadministration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely. Hydroxyurea undergoes metabolism via non-CYP mediated metabolism and is not a substrate of P-gp.
Imipenem/Cilastatin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Renal clearance of unchanged drug occurs via glomerular filtration and to a lesser extent, active tubular secretion for both imipenem (when administered with cilastatin), and cilastatin.
Insulin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.
Ipratropium bromide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. A small proportion of an inhaled ipratropium dose is systemically absorbed (6.9%). Metabolism is via ester hydrolysis and conjugation.
Isoflurane	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Isoflurane is almost exclusively eliminated unchanged by the lungs.
Kanamycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Kanamycin is predominantly eliminated unchanged via renal glomerular filtration.

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Green Interactions
Labetalol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Labetalol is mainly glucuronidated by UGTs 1A1 and 2B7. Weekly administration of rifapentine did not reduce the exposure of the UGT1A1 substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Lactulose	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Metabolism of lactulose to lactic acid occurs via gastro-intestinal microbial flora only.
Lamivudine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Lamivudine is eliminated renally.
Levofloxacin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Levofloxacin is metabolised to a very small extent and is eliminated renally mainly by glomerular filtration and active secretion (possibly OCT2).
Levonorgestrel (IUD)	Coadministration with a levonorgestrel intra-uterine device (IUD) has not been studied but there is little potential for an interaction given the local mechanism of action of levonorgestrel.
Levothyroxine	Coadministration has not been studied but based on metabolism and clearance, a clinically significant interaction is unlikely. Levothyroxine is metabolized by deiodination (by enzymes of deiodinase family) and glucuronidation. Weekly administration of rifapentine did not reduce the exposure of the pure UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Lidocaine (Lignocaine)	Coadministration has not been studied but based on metabolism and clearance, a clinically significant interaction is unlikely. CYP1A2 is the predominant enzyme involved in lidocaine metabolism in the range of therapeutic concentrations with a minor contribution from CYP3A4. Isoniazid/rifapentine is not expected to induce CYP1A2 significantly.
Magnesium supplements	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Magnesium is eliminated in kidney, mainly by glomerular filtration.
Melarsoprol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely, although due to the lack of available data, vigilance is required as it is unknown whether urinary metabolites of melarsoprol, such as arsenic, are excreted via active renal mechanisms. However, a clinical study has reported that urinary pharmacokinetic parameters are not predictive of toxicity or therapeutic efficacy.
Meropenem	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Meropenem is primarily eliminated by the kidney and in vitro data suggest that it is a substrate of the renal transporters OAT3>OAT1. Isoniazid/rifapentine do not interfere with this elimination pathway.
Metformin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Metformin is primarily eliminated by the kidney via OCT2 and MATE1. Isoniazid/rifapentine do not interfere with this elimination pathway.
Methotrexate	Coadministration has not been studied but based on metabolism and clearance there is little potential for an interaction. Methotrexate is predominantly eliminated unchanged via the kidneys, with minimal metabolism.
Methyldopa	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Methyldopa is excreted in urine largely by glomerular filtration, primarily unchanged and as the mono-O-sulfate conjugate.

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Green Interactions
Metoclopramide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Metoclopramide is partially metabolized by CYP450 system (mainly CYP2D6). In vitro data indicate that rifapentine does not induce CYP2D6 significantly. Isoniazid has no inhibitory/inducing effects on CYP2D6.
Metronidazole	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. More than 50% of the administered dose is excreted in the urine as unchanged metronidazole.
Misoprostol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Misoprostol is predominantly metabolised via fatty acid oxidising systems and has no effect on the CYP450 enzyme system.
Morphine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Morphine is mainly glucuronidated to morphine-3-glucuronide (UGT2B7>UGT1A1) and, to a lesser extent, to the pharmacologically active morphine-6-glucuronide (UGT2B7>UGT1A1). Weekly administration of rifapentine did not reduce the exposure of the pure UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Moxifloxacin	The effect of high-dose intermittent rifapentine on the pharmacokinetics of moxifloxacin was studied in patients with pulmonary tuberculosis. Patients were randomized to a continuation-phase regimen of 400 mg moxifloxacin and 900 mg rifapentine twice weekly or 400 mg moxifloxacin and 1,200 mg rifapentine once weekly. Rifapentine increased the clearance of moxifloxacin by 8% during antituberculosis treatment compared to that after treatment completion without rifapentine. This effect is not considered to be clinically relevant (*Zvada S et al. Antimicrob Agents Chemother 2012*). Isoniazid is unlikely to affect moxifloxacin as it does not inhibit or induce UGTs.
Multivitamins	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.
Naloxone	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Naloxone is mainly glucuronidated. the weekly administration of rifapentine did not reduce the exposure of the pure UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Neostigmine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Neostigmine is thought to undergo a degree of hepatic metabolism, although the mechanisms are unknown. However, as metabolism also occurs via hydrolysis by cholinesterase and up to 50% of a dose is excreted unchanged via the kidneys, there is little potential for clinically significant interaction with antiretrovirals via liver enzyme modification.
Nicotinamide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Nicotinamide is metabolized by nicotinamide methyltransferase to N-methylnicotinamide which is then metabolized by xanthine oxidase and aldehyde oxidase. Isoniazid/rifapentine does not interfere with this elimination pathway.
Nitrofurantoin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. 30-40% of a nitrofurantoin dose is eliminated unchanged via the kidneys, with a small proportion metabolized to aminofurantoin.
Nystatin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Systemic absorption of nystatin from oral or topical dosage forms is not significant, therefore no drug interactions are expected.

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Drug Interaction Notes for Weekly Isoniazid/Rifapentine

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Green Interactions
Omeprazole	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Coadministration of isoniazid/rifapentine with medicinal products that alter gastric pH would not be expected to affect isoniazid/rifapentine absorption (*Lin MY et al. Int J Tuberc Lung Dis 2010*).
Oxytocin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Elimination of oxytocin occurs via the liver, kidney, functional mammary gland and oxytocinase. The plasma half-life is approximately five minutes.
Para-aminosalicylic acid	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Para-aminosalicylic acid is predominantly eliminated unchanged via the kidneys.
Penicillins	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Penicillins are mainly eliminated in the urine (20% by glomerular filtration and 80% by tubular secretion via OAT).
Phytomenadione (Vitamin K)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Metabolism of phytomenadione is thought to involve CYP4F2 and glucuronidation. Renal elimination of phytomenadione is minimal.
Piperacillin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Piperacillin is eliminated renally via glomerular filtration and active secretion by OAT1/3.
Potassium	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as potassium is eliminated renally.
Promethazine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Promethazine is metabolized by CYP2D6. Isoniazid/rifapentine does not inhibit of induce CYP2D6.
Propranolol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Propranolol is metabolized by 3 routes (aromatic hydroxylation by CYP2D6, N-dealkylation followed by side chain hydroxylation via CYPs 1A2, 2C19, 2D6, and direct glucuronidation). Isoniazid/rifapentine does not inhibit of induce CYP2D6 and is not expected to induce CYP1A2 significantly. Rifapentine induces CYP2C19 but this effect is expected to be mitigated by the inhibitory effect of isoniazid on CYP2C19. Finally, weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.
Protamine sulphate	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. The metabolism of protamine has not been fully elucidated, however protamine complexed with heparin is thought to be partially metabolised by fibrinolysin.
Pyrazinamide	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Pyrazinamide is mainly metabolized by xanthine oxidase.
Pyridoxine (Vitamin B6)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Pyridoxine is absorbed from the GI tract and is converted to the active form pyridoxal phosphate. It is excreted in the urine as 4-pyridoxic acid.
Pyrimethamine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Data on the exact pathways of metabolism of pyrimethamine are limited but few interactions have been described with this drug.
Ranitidine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Coadministration of isoniazid/rifapentine with medicinal products that alter gastric pH would not be expected to affect isoniazid/rifapentine absorption (*Lin MY et al. Int J Tuberc Lung Dis 2010*).

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

Please check www.hiv-druginteractions.org/prescribing_resources for updates to this document.

Comedication	Notes on Green Interactions
Retinol (Vitamin A)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Vitamin A esters are hydrolysed by pancreatic enzymes to retinol, which is then absorbed and re-esterified. Some retinol is stored in the liver. Retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid.
Salbutamol	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Salbutamol is metabolized to the inactive salbutamol-4'-O-sulphate.
Sevoflurane	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely as sevoflurane is almost exclusively eliminated unchanged by the lungs.
Spironolactone	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Spironolactone is partly metabolized by the flavin containing monooxygenases.
Stavudine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Stavudine is mostly eliminated in the urine as unchanged drug.
Streptokinase	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Like other proteins, streptokinase is metabolised proteolytically in the liver and eliminated via the kidneys.
Streptomycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Streptomycin is excreted rapidly in the urine by glomerular filtration.
Sulfadoxine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Sulfadoxine is primarily cleared renally through glomerular filtration.
Suramin sodium	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Suramin appears to be eliminated predominantly unchanged via renal glomerular filtration.
Suxamethonium	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Suxamethonium is hydrolysed by plasma cholinesterase.
Tenofovir-DF	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. No significant interaction was observed when tenofovir-DF (300 mg once daily) and another strong inducer rifampicin (600 mg once daily) were coadministered. Tenofovir AUC, Cmax and Cmin decreased by 12%, 16% and 15%, respectively and rifampicin pharmacokinetics were comparable to historical controls (*Droste JAH et al. Antimicrob Agents Chemother. 2005*).
Tetracyclines	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Tetracyclines are eliminated unchanged primarily by glomerular filtration.
Thiamine (Vitamin B1)	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.
Thiopental	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Although pentobarbital (a potent inducer of hepatic microsomal drug metabolism) is formed during thiopental metabolism, levels do not reach the therapeutic range and isoniazid/rifapentine pharmacokinetics are unlikely to be affected significantly by coadministration with thiopental.
Trimethoprim/ Sulfamethoxazole	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Trimethoprim and sulfamethoxazole are eliminated by the kidneys through glomerular filtration and tubular secretion.
Vancomycin	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Vancomycin is predominantly eliminated unchanged via renal glomerular filtration.

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dose adjustment or close monitoring.
- Potential weak interaction. No *a priori* dosage adjustment is recommended.

Interactions details are for the combination of isoniazid plus rifapentine and are not applicable to other rifamycins.

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Comedication	Notes on Green Interactions
Vecuronium	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Vecuronium is partly deacetylated and partly cleared in the bile as parent compound.
Zidovudine	Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Zidovudine is partly eliminated by glucuronidation. Weekly administration of rifapentine did not reduce the exposure of the UGT substrate raltegravir (*Weiner M et al. J Antimicrob Chemother 2014*). Isoniazid does not inhibit or induce UGTs.

Colour Legend

No clinically significant interaction expected.

These drugs should not be coadministered.

Potential interaction which may require a dose adjustment or close monitoring.

Potential weak interaction. No *a priori* dosage adjustment is recommended.